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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

please ent 2/10/2002

In re application of

Nobuhiko OGURA

Appln. No.: 09/373,585

Confirmation No.

Group Art Unit: 1655

Filed: August 13, 1999

Examiner: F. Lu

For: TEST PIECE, METHOD OF AND APPARATUS FOR MANUFACTURING THE TEST PIECE AND METHOD OF AND SYSTEM FOR READING THE SAME

AMENDMENT UNDER 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated August 3, 2000, please amend the above-identified application as follows:

IN THE SPECIFICATION:

Page 4, first full paragraph, please delete in its entirety and replace with the following new paragraph.

A1

Accordingly, still another object of the present invention is to provide a method of and a system for reading the test piece which allows easier and less expensive biological analysis such as DNA analysis, immunological analysis and the like.

Page 5, third full paragraph, please delete in its entirety and replace with the following new paragraph.

A2

Preferably the strip-like substrate is a flexible member in a continuous length from the viewpoint of ease of manufacture and mass productivity.

Page 15, first full paragraph, please delete in its entirety and replace with the following new paragraph.

A3

Further such reduction of cost makes it feasible application of the test piece to screening of a human or an animal infected with pathogenic bacterias or viruses, screening of cancerous cells, and the like.

IN THE CLAIMS:

Cancel claim 2 without prejudice or disclaimer.

Please enter the following amended claims:

A4

1. (Amended). A test piece for use in biological analysis of a sample comprising:

a strip-like substrate comprising a plurality of known specific binding agents which are different from each other, each of said plurality of binding agents being applied across an entire width of the strip-like substrate at predetermined intervals and spaced apart from another of said plurality of known binding agents in a longitudinal direction of the strip-like substrate, wherein said substrate is flexible.

A5

6. (Amended). An apparatus for manufacturing a test piece for use in biological analysis of a sample organism comprising a strip-like substrate bearing thereon numbers of known specific binding agents which are different from each other and are arranged in a line at predetermined intervals in the longitudinal direction of the strip-like substrate, the apparatus comprising:

a plurality of applicators arranged at predetermined interval in a first direction relative to a sheet-like substrate each of said plurality of applicators respectively operable to apply one of the plurality of known specific binding agents on the sheet-like substrate,

a conveyor which conveys the plurality of applicators or the sheet-like substrate relative to each other in a second direction which is substantially perpendicular to the first direction while the applicators apply the plurality of known specific binding agents, thereby applying the plurality of known specific binding agents in lines which extend in the second direction and are arranged at predetermined intervals in the first direction, and

a cutting means which cuts the sheet-like substrate bearing thereon the plurality of specific binding agents in the first direction into a plurality of strips.

A6

14. (Amended). A system for reading a test piece comprising a strip-like substrate bearing thereon numbers of known specific binding agents which are different from each other and are arranged in a line at predetermined intervals in the longitudinal direction of the strip-like substrate, the system comprising:

an exciting light source which projects, onto the test piece applied with substrate derived from a sample organism labelled with fluorescent dye, exciting light which excites the fluorescent dye,

A6 CONT.

a conveyor which conveys the strip-like substrate or the exciting light source to impart relative movement between the strip-like substrate and the exciting light source, said relative movement being along a single axis;

a photodetector which detects fluorescence emitted from the test piece upon excitation by the exciting light, and

an analysis means which relates the result of detection of the fluorescence with the positions in which the fluorescence is emitted and thereby determines the specific binding agent(s) on the test piece with which the substance derived from the sample organism is hybridized.

A7

19. (Amended) A system as defined in Claim [19] 17 further comprising a scanning system which causes the exciting light to linearly scan the strip-like test piece in the longitudinal direction thereof.

Kindly add the following new claims:

A8

--20. The system defined in claim 19, wherein the scanning system scans in only the longitudinal direction of the strip-like test piece.

A8 cont.

21. The system of claim 6, wherein the binding agents are formed in continuous lines across the sheet-like substrate.--

REMARKS

This amendment, submitted in response to the Office Action dated August 3, 2000, is believed to be fully responsive to each point of rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-19 remain pending in the application. Claims 4-5 and 8-13 have been withdrawn from further consideration at this time, pursuant to the provisional Response to Restriction Requirement of July 25, 2000. Applicant hereby affirms the rejection.

Claims 1-3, 6-7 and 14-19 have been considered on the merits. Claims 6-7 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-3 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Stephens et al. ("Transcriptional Repression of the GLUT4 and C/EBP Genes in 3T3-L1 Adipocytes by Tumor Necrosis Factor α*", hereafter "Stephens"). Claims 6-7 have been rejected under 35 U.S.C. § 103 as being unpatentable over Klebe ("Cytoscribing: A Method for Micropositioning Cells and the Construction of Two- and Three-Dimensional Synthetic Tissues") in view of Proudnikov et al. ("Immobilization of DNA in Polyacrlamide Gel for the Manufacture of DNA and DNA-Oligonucleotide Microchips", hereafter "Proudnikov"). Claims 14-19 have been rejected under 35 U.S.C. § 102(e) as being anticipated or in the alternative as being obvious under 35 U.S.C. § 103 in view of Stern et al. (U.S.P. 5,631,734, hereafter "Stern"). Applicant hereinabove amends

the claims to describe the invention more particularly. Applicant further submits the following arguments in traversal of § 112 and the prior art rejections.

With regard to the rejection under Section 112, the amended claim 6 describes first and second directions as substantially perpendicular to each other. In view of the specification and Fig. 3, one skilled in the art would understand the arrangement of the conveyor and the application devices with reference to the first and second directions.

Turning to the prior art rejections, the present invention relates to a test piece for biological analysis using cDNA samples, an apparatus used to form such a test piece, and an apparatus to read a test piece once biological reactions have occurred on the test piece. Conventional test pieces comprise a microarray of cDNA samples spaced very closely together, as shown in Fig. 5. The samples are individually pipeted onto the chip, using a needle-like coating chip for example. Since several hundreds of thousands of samples may be required for an analysis, the conventional test piece requires a long time and significant expense to manufacture. When the cDNA samples on the test piece are reacted with a gene sample, respective labeling dyes for each are detected using a photodetector. In view of the close proximity of the samples on the microarray, the accuracy of the two dimensional scan of the photodetector on the microchip array becomes very critical, resulting in a time-consuming and expensive reading process. Applicant's invention overcomes the above deficiencies.

Referring to Fig. 1, the test piece of the present invention includes a flexible substrate 12 bearing known cDNAs 13 which are known binding agents. The cDNAs differ from each other and are arranged at predetermined intervals on the order of several hundred μm in the

longitudinal direction of the substrate. The test piece is cut from a larger substrate 10, as shown in Fig. 2. The larger array 10 is fabricated using the apparatus illustrated in Fig. 3.

Referring to Fig. 3, a conveyor 40 rolls out the substrate 12' in the direction Y, and an applicator 30 having a number of application ports 31 are arranged at predetermined intervals in the direction perpendicular to the direction of travel Y. The applicators form lines of the binding agents along a width of the substrate as the substrate is conveyed. A supply section 20 includes cDNA reservoirs 21 which are respectively connected to the application ports 31. A cutter 61 moves in a direction substantially perpendicular to the direction Y to cut strips comprising the test piece 11.

Fig. 4 illustrates an apparatus for reading a test piece in accordance with a preferred embodiment of the invention. A conveyor 240 conveys the test piece along its longitudinal direction indicated by the arrow X. By providing conveyance along the single axis, the apparatus and scanning of the hybridized samples can be simplified. The binding agent and applied organism are respectively labeled with dyes a and b, and first and second light sources 210 and 220 emit light which respectively excite the dyes a and b. The light passes through an optical system, causes fluorescence in the sample recorded on the substrate which is filtered by device 260, picked up by photodetector 231 and processed by an analysis device 250. The analysis device is further operable to determine a difference between the fluorescence level between the two dyes. Because the types and sequences of cDNAs on the test piece are known, the analysis means can determine the cDNAs which exist in a first sample and do not exist in the

second sample and whose which do not exist in the first sample and exist in the second to provide genetic analysis.

Turning to the cited art, Stephens relates to a study of transcripted RNAs from a nucleic treated with a control and a TNF sample to hybridize with cDNAs. Though the Examiner has characterized the cDNAs as being immobilized on a nylon membrane, it is ambiguous that the cDNAs were applied as the Examiner suggests. Rather, it appears that the 3T3-L1 genomic DNA was the component immobilized on the substrate. It is observed that RNA isolation and analysis were performed using electrophoresis, resulting in the separation of GLUT 1, GLUT 4, 442, etc. components by molecular weight. See page 21840, col. 2, *RNA Isolation and Analysis*.

Klebe relates to cytoscribing, including the application of a fibronectin to a strata using an ink jet printer by replacing the ink in the ink cartridge of the printer with the fibronectin solution. The fibronectin is used for cell adhesion and to build cell matrices.

Proudnikov relates to immobilization of DNA in polyacrylamide gel for manufacture of microchips. No express teaching of a cutting implement for providing the microchips is discussed.

Stern relates to an apparatus for reading information formed on a substrate using three-dimensional scanning.

The Examiner maintains that independent claim 1 is anticipated by Stephens. However, as amended, claim 1 describes that each of a plurality of binding agents is applied to the substrate across a width of the substrate. In Stephens, it is ambiguous as to whether the binding proteins,

e.g. GLUT 1/GLUT4 are applied to a substrate or separated out by molecular weight through a process of electrophoresis. Applicant argues that any ambiguity in the teaching must be construed against the Examiner since mere possibilities of the existence of a claim feature in a reference do not support an anticipation rejection. Moreover, claim 1 describes that the binding agent is applied across an entire width of the strip. To the extent that binding agents are applied in Stephens, there is no requirement that they be formed across an entire width as described in claim 1. This aspect of the test piece is significant as it is the by-product of the ability to produce several strips from a larger substrate in large quantities, as compared with individual application of different binding agents on a substrate, which is a more time consuming process. Therefore, claim 1 is not anticipated for at least these reasons. Claim 3 is further patentable based on their dependency.

The Examiner maintains that independent claim 6 is unpatentable over the combination of Klebe and Proudnikov. Applicant argues that the Examiner's rejection is not supported for at least three reasons.

First, as an initial matter, the Examiner has not offered a reason as to why it would be obvious to combine the cell matrix construction described in Klebe with the immobilization of DNA described in Proudnikov. The Examiner states that it would be obvious to load fibronectin onto a sheet-like substrate and then maintains that it would be obvious to cut the substrate into microarrays. However, there is no motivation in the art for the Examiner's suggestions. Rather, the motivation to construct a small test piece from a larger substrate is only taught by Applicant's own disclosure.

Second, even though the Examiner points out that Proudnikov includes microarrays, there is no teaching that the microarray is obtained as a cut off portion of a larger substrate. The Examiner has conceded that no such cutting member is included in Klebe and also fails to identify where such a cutting member is included in Proudnikov. The microarray need not be formed from a cut from a larger substrate but may simply have been originally produced on a small substrate platform. As discussed above, any ambiguities in the reference must be construed against the Examiner since possibilities do not support prior art rejections.

Third, claim 6 describes that binding agents are applied in lines which extend in a second direction, the direction of conveyance of the substrate. By contrast, Klebe uses a printer that outputs a fibronectin in the form of text characters rather than lines. This difference is significant since the lines of binding agents across a substrate permit multiple uniform test pieces to be cut from the substrate. By contrast, the text characters formed by the ink jet mechanism of Klebe result in gaps and irregularities that would make the substrate inappropriate for forming multiple uniform test pieces. Therefore, claim 6 is patentable for at least these reasons. Because these features were previously included in the originally filed claims, should the Examiner cite an additional reference against claim 6, the rejection must be made on a non-final basis.

The Examiner maintains that independent claims 14 and 19 are either anticipated or rendered obvious by Stern.

With respect to claim 14, as amended, this claim describes a conveyor that imparts relative movement between the strip and the light source along a single axis. By contrast, the stage of Stern moves along multiple axes, requiring expensive control mechanisms and the risk

of reduced accuracy in scanning and light detection. Therefore, claim 14 is patentable for at least this reason.

With respect to claim 17, this claim describes an analysis device that determines a difference in fluorescence values between two samples for genetic analysis. Stern does not include such a feature for determining a difference value. Therefore, claim 17 is unpatentable for at least this reason.

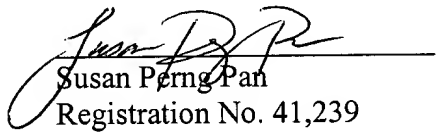
The remaining claims are patentable based on their dependency.

Applicant have added claims 20-21 to describe features of the invention more particularly.

In view of the above, Applicant submits that claims 1, 3, 6-7, 14-19 and new claims 20 and 21 are in condition for allowance. Therefore it is respectfully requested that the subject application be passed to issue at the earliest possible time. The Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



Susan Perng Pan
Registration No. 41,239

SUGHRUE, MION, ZINN,
MACPEAK & SEAS, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060

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